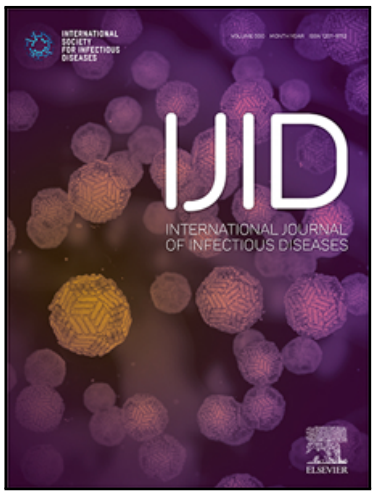
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis

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Highlights:

- The COVID-19 VE in real-world settings.
- The COVID-19 VE for fully and partially vaccinated individuals.
- The COVID-19 VE for health care workers, the elderly, and adults.
- The effectiveness of different COVID-19 vaccine brands.

Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis

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Abstract

Objectives: To estimate the COVID-19 vaccine effectiveness (VE) against concerned outcomes in real-world settings.

Methods: We included studies reported the COVID-19 VE from August 6, 2020, to October 6, 2021. We estimated the summary VE with 95% confidence intervals (95% CIs) against disease related to COVID-19. The results were presented in forest plots. Predefined subgroup analysis and sensitivity analysis was also performed.

Results: 51 records were included in this meta-analysis. In the full vaccination, the VE against SARS-CoV-2 infection, COVID-19 related hospitalization, admission to ICU, and death were 89.1% (95% CI, 85.6 to 92.6), 97.2% (95% CI, 96.1 to 98.3), 97.4% (95% CI, 96.0 to 98.8) and 99.0% (95% CI, 98.5 to 99.6), respectively. It showed that the VE against infection for general population aged 16 years or older, the elderly and health care workers (HCWs) were 86.1% (95% CI, 77.8 to 94.4), 83.8% (95% CI, 77.1 to 90.6) and 95.3% (95% CI, 92.0 to 98.6), respectively. For full vaccination against infection, 91.2% effectiveness of the Pfizer-BioNTech vaccine and the 98.1% effectiveness of Moderna vaccine were observed, while 65.7% effectiveness of the CoronaVac were reported.

Conclusions: The COVID-19 vaccines are highly protective against SARS-CoV-2 related diseases in the real-world settings.

Keywords: COVID-19, SARS-CoV-2, Vaccine, Effectiveness, Real-world

Introduction

Globally, as of 15 October 2021, there have been more than 239.4 million confirmed cases of Coronavirus disease 2019 (COVID-19), including over 4.8 million deaths(WHO, 2021b). Science the outbreak of COVID-19, several vaccines have been tested and granted for emergency use authorization. Phase III trials reported high vaccine effectiveness (VE) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with these vaccines, such as 70.4% effectiveness of the ChAdOx1 nCoV-19 (AZD1222; Oxford-AstraZeneca) vaccine(Voysey et al., 2021), 95% effectiveness of the BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) vaccine(Skowronski and De Serres, 2021), 94.1% effectiveness of the mRNA-1273 (Moderna) vaccine(Baden et al., 2021), and 50.7% effectiveness of the absorbed COVID-19 (inactivated) vaccine (Corona Vac)(Palacios et al., 2020). Given that the outcomes in clinical trials may be influenced by various study settings, it is necessary to estimate the effectiveness of vaccines rolled out to the public in the real-world. Recently, a series of studies have reported real-world VE all over the world. A nationwide mass vaccination setting in Israel showed 92% effectiveness for documented infections after the second dose of the BNT162b2 vaccine(Dagan et al., 2021). The UK government has adopted a strategy of delaying the second dose to increase the vaccine coverage, which suggested a 51.4% VE against SARS-CoV-2 infections after 1 dose of the BNT162b2 vaccine(Chodick et al., 2021). 73% effectiveness against COVID-19 cases was observed among the elderly after vaccination with 1 dose of the ChAdOx1 vaccine in England(Lopez Bernal et al.,

2021). In Chile, the Sinovac vaccine rolled out to the general population aged 16 or older showed an effectiveness of 16.13% after the first dose and 66.96% after the second dose.(Salud., 2021) The World Health Organization (WHO) notes that there is an urgent need for COVID-19 VE against several major outcomes, including symptomatic COVID-19, severe diseases, and death related to COVID-19(Patel et al., 2021). Therefore, we conducted this review and meta-analysis to estimate the COVID-19 VE against concerned outcomes in real-world settings based on the latest evidence.

Methods

Search and inclusion criteria

For this literature review and meta-analysis, we searched systematically in PubMed, using the terms “COVID-19” or “SARS-CoV-2” and “vacc*” and “eff*” for articles published August 6, 2020 (Deplanque and Launay, 2021) to October 6, 2021 in countries where are vaccinated. In addition, we searched major news media platforms to track reports from governments and health authorities around the world evaluating the effectiveness of the COVID-19 vaccine. The review process is described in detail in Figure 1.

Observational study (cohort, case-control, test-negative case-control) were included. Studies reporting exclusively on the immunogenicity of COVID-19 vaccine, review articles, data only in abstract form, ecological study, mathematical modeling analysis studies were excluded. If two or more articles and reports presented results from the

same dataset, all articles that included unique data points by the vaccine, study population, or vaccination status were included. In situations where findings in one article were a subset of findings from another article (e.g., study sites and population) only the most comprehensive article was included in the overall analysis, but the subset was included in subgroup analysis. At least 2 reviewers examined articles to confirm inclusion criteria were satisfied and to reach consensus when necessary.

Data were extracted by two independent authors in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)(Page et al., 2021) and the checklist was presented in Supplement table1. We abstracted summary VE, stratified VE estimates by COVID-19 vaccine against a range of SARS-CoV-2 outcomes (confirmed SARS-CoV-2 infection with reverse transcription-polymerase chain reaction (rt-PCR), and COVID-19 related hospitalization, admission to the ICU and severe or critical hospitalization, and death) in partial and full vaccination (in view of the status of partial and full vaccination of individuals varied with the recommendations of the health authorities in different countries and regions, we relied on those reported in the literature and included analysis of the results.), vaccine brand and study population; characters of the studies, such as study design, study population, and sample size, into a Microsoft Excel database.

Data analysis

Descriptive statistics and percentages were calculated for the article attributes. We estimated the real-world effectiveness of COVID-19 vaccines against a range of

SARS-CoV-2 outcomes in partial and full vaccination status, vaccinated population, and vaccines brand. Estimates of VE expressed as percentage (%) as well as their 95% confidence intervals (95% CIs) were derived from the effect measures (odds ratios, relative risks, hazard ratios, and incidence rate ratios) using VE = [1-effect measure] × 100. VE estimates > 0% suggest a protective effect. The results were presented in forest plots.

Heterogeneity of outcomes across studies was assessed with the I^2 statistics and be quantified as low (≤ 25%), moderate (25% ~ 50%), and high (>50%). A random-effects model was used when I^2 statistics > 25% in the data. Otherwise, fixed-effects model was chosen. Conducting stratified meta-analyses explore potential sources of study heterogeneity.

The Newcastle-Ottawa scale (NOS) (range from 0 to 9 points) was used to assess the quality of included observational studies, and a higher total NOS score suggests better quality(Wells. et al.). The influence of inclusion of a study on the results of this meta-analyses was assessed using sensitivity analysis. Additionally, we used Egger's test and a funnel plot of the standard error, sampling variance, and the inverse of the standard error and sampling variance to evaluate the publication bias with 10 or more included articles. Analyses were conducted in R software (version 4.1.0; The R Foundation) using the metafor package for meta-analyses('metafor', 2021).

Results

Characteristics of the Studies

For this literature review, we identified and screened 13018 records, of which 13016 were in PubMed, and 2 reports from the official website of the government health department.

12645 were not relevant to the research question based on title and were excluded (Figure 1). Abstracts were reviewed for the remaining 115 articles and 2 reports. 59 articles were read in full; an additional 7 were excluded because they did not meet our methodological inclusion criteria. One report did not provide information on the time span of vaccination, age, and health status of the vaccinated persons, and was therefore excluded. In total, 50 articles and 1 report were included from 14 countries including 38821141 individuals.

All the literature were published in 2021 with high quality (range from 5 to 8 scores)(Wells. et al.) (Supplement table2). 39 were cohort studies, 8 were test-negative case-control studies, and 4 were case-control studies. The included studies contained 5 brands of COVID-19 vaccines: Pfizer-BioNTech (46 articles), Moderna (19 articles), Oxford-AstraZeneca (10 articles), CoronaVac (5 articles), and Janssen [Johnson & Johnson]) (1 articles). Most articles presented VE estimation for fully vaccinated and partly vaccinated (34 articles, 66.7%), 11 articles (21.6%) only presented effectiveness of partly vaccinated.

Vaccine effectiveness for full vaccination

We estimated the effectiveness of COVID-19 vaccines against a range of SARS-CoV-2 outcomes. A total of 35 articles reported the VE against SARS-CoV-2

infection among fully vaccinated people, and the summary VE was 89.1% (95% CI, 85.6 to 92.6) for prevention of SARS-CoV-2 infection (Figure 2). In addition, 15, 4, and 8 articles of included studies estimated the VE against COVID-19 related hospitalization, ICU admission or severe disease, and death, respectively. The results showed 97.2% (95% CI, 96.1 to 98.3) for the prevention of hospitalization, 97.4% (95% CI, 96.0 to 98.8) for the prevention of ICU admission or severe disease, and 99.0% (95% CI, 98.5 to 99.6) for the prevention of COVID-19 related death (Figure 3). The Egger's test and funnel plots showed no publication bias of the VE against SARS-CoV-2 infection (*t* value of Egger's test = -2.91, *P* = 0.0988) among fully vaccinated individuals, while there was publication bias of the VE against COVID-19 related hospitalization (*t* value of Egger's test = -2.91, *P* = 0.006). (Supplement figure 1B). After correcting for publication bias with Trim and Fill methods, the summary VE against COVID-19 related hospitalization among fully vaccinated individuals was 97.2% (95% CI, 94.4 to 100.0) (Supplement figure 1C). For sensitivity analysis, it suggested lower VE against COVID-19 related hospitalization (93.0% (95% CI, 91.0 to 96.0)) and ICU admission and severe disease (89.0% (95% CI, 76.0 to 100.0)) when deleting the results conducted by Eric J Haas, et al(Haas et al., 2021). (Supplement figure 2-3).

Vaccine effectiveness for partial vaccination

In the partly immunized status, 38, 12, 3, and 8 articles of included studies reported VE against SARS-CoV-2 infection, COVID-19 related hospitalization, ICU admission or severe disease, and death, respectively. The summary VE was 68.8% (95% CI, 60.1

to 77.5) for the prevention of SARS-CoV-2 infection and 67.8% (95% CI, 51.6 to 83.9) for the prevention of hospitalization, 66.4% (95% CI, 25.9 to 100.0) for the prevention of admission to the ICU and severe disease, and 58.4% (95% CI, 28.0 to 88.7) for the prevention of COVID-19 related death (Supplement figure 4-5). The Egger's test and funnel plots suggested no publication bias of the VE against SARS-CoV-2 infection (*t* value of Egger's test = -1.31, *P* = 0.1956) and hospitalization (*t* value of Egger's test = -0.28, *P* = 0.7839) for partially vaccinated individuals. (Supplement figure 6). For sensitivity analysis, it suggested higher VE against SARS-CoV-2 infection (75.0% (95% CI, 71.0 to 80.0)) among the partially vaccinated individuals when deleting the results of the Corona Vac vaccine reported by Ministerio de salud(Salud., 2021) (Supplement figure 7-8).

Subgroup analysis

To estimate the COVID-19 VE for prevention SARS-CoV-2 infection with rt-PCR in fully vaccinated status in different populations. We conducted an analysis in the predefined subgroup of the elderly (aged 60 years or older), health care workers (HCWs), and general population (adults aged 16 years or older). There were 15, 17, and 11 articles including 4 brands of COVID-19 vaccines (Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and CoronaVac) respectively presenting the VE against SARS-CoV-2 infection among the elderly, HCWs, and the general population. The summary VE were 83.8% (95% CI, 77.1 to 90.6) among the elderly, 95.3% (95% CI, 92.0 to 98.6) among HCWs, and 86.1% (95% CI, 77.8 to 94.4) among the general population (Figure 4).

We also estimated VE of different vaccine brands among fully vaccinated people. For the Pfizer-BioNTech vaccine, a total of 23 articles reported the VE for full vaccination. The summary VE were 91.2% (95% CI, 87.9 to 94.5) against SARS-CoV-2 infection (Figure 5), 97.6% (95% CI, 96.5 to 98.7) against COVID-19 related hospitalization, and 98.1% (95% CI, 96.3 to 99.9) against COVID-19 related death (Figure 6). There were 5 and 3 articles estimating the effectiveness against of SARS-CoV-2 infection of the Moderna and CoronaVac vaccine. The Moderna vaccine presents a highest VE against infection, with a summary VE of 98.1 % (95% CI, 96.0 to 100.0). The VE against infection of CoronaVac vaccine were 65.7% (95% CI, 63.0 to 68.5) (Figure 5). Only 1 article in India reported the 88.6% (95% CI, 81.6 to 92.4) effectiveness against infection of the fully vaccinated Oxford-AstraZeneca vaccine (Zacay et al., 2021). Besides, 8 articles reported the VE of the Oxford-AstraZeneca vaccine among partially vaccinated people, and the summary VE was 81.8% (95% CI, 67.1 to 96.6) (Supplement figure 9). No significant publication bias was detected for subgroup analysis ($P > 0.05$).

Discussion

In this review including 51 latest records from 14 countries reported on the effectiveness of COVID-19 vaccines, we estimated the VE against disease with laboratory-confirmed SARS-CoV-2 infection, COVID-19 related hospitalization, admission to ICU, and death. We presented the estimates of VE against infection with subgroup analyses for vaccine brands, vaccinated population, and vaccinated status.

The results suggested that the vaccines currently approved for use have a good protective effect against the major outcomes related to COVID-19, especially for critical outcomes.

It's noted that there was high heterogeneity for the summary VE against SARS-CoV-2 infection among fully vaccinated individuals. In addition to the actual effectiveness of the different vaccines, population effectiveness evaluation depends on a series of factors, such as the vaccinated population, the severity of the epidemic, the completeness and validity of the data sources, study design and potential methodological biases (Patel et al., 2021). Therefore, we performed subgroup analysis and sensitivity analysis to explore the potential heterogeneity. Consistent with the results of phase III clinical trials, the effectiveness of different vaccines against confirmed infection in real-world conditions varied(Baden et al., 2021, Palacios et al., 2020, Skowronski and De Serres, 2021, Voysey et al., 2021). Synthesized evidence from different study settings showed 91.2%, 98.1%, and 65.7% effectiveness of the Pfizer-BioNTech vaccine, the Moderna vaccine, and the Corona Vac, respectively. For full vaccination, lower VE against COVID-19 related hospitalization and severe disease were observed when deleting the results conducted by Eric J Haas, et al(Haas et al., 2021). The study with a high quality revealed that two doses of BNT162b2 are highly effective across all age groups in Israel based on nationwide surveillance data. Sensitivity analysis showed higher VE after omitting the results of the Corona Vac.(Hitchings et al., 2021, Salud., 2021) The VE of Corona Vac, an inactivated whole virus vaccine, may be influenced in the settings of high SARS-CoV-2 Gamma

variant transmission, whether in Brazil or Chile.(Jara et al., 2021, Palacios et al., 2020, Ranzani et al., 2021) Similarly, VE is closely related to vaccination status. Subgroup analysis by vaccination status revealed that 66.8%, 67.8%, 66.4 and 58.4% effectiveness of partial vaccination against disease with confirmed infection, COVID-19 related hospitalization, severe diseases, and death, respectively, despite less effective than full vaccination. Therefore, this finding supports the proposal across many countries of extending dosing interval to optimize the vaccine coverage with the increasing number of new infections and the spread of SARS-CoV-2 variants(Chodick et al., 2021, Krutikov et al., 2021, Shrotri et al., 2021). Besides, several studies showed higher VE for longer periods of time since vaccination, whether for partial or full vaccination. (Jones et al., 2021, Rudolph et al., 2021, Zaqout et al., 2021)

Given the highest mortality observed in the elderly of long-term care facilities and higher exposure risk for health care workers(Team, 2020, Wu and McGoogan, 2020, Zhou et al., 2020), many countries have prioritized both high-risk groups for vaccinations(Britton et al., 2021, Lopez Bernal et al., 2021). However, elderly patients are less represented in clinical trials which mainly enrolled young population(Prendki et al., 2020). We synthesized evidence in real-world by vaccinated population. The most protective effect was seen in the health care workers (VE = 95.3%), while less VE was observed in the elderly (VE = 83.8%). Due to immunosenescence and comorbidities, the elderly are more susceptible to infections and have poor responses to vaccination(Brosh-Nissimov et al., 2021, Ciabattini et al., 2018, Frasca et al., 2010,

McElhaney et al., 2013). Therefore, more measures for the elderly than vaccination need to be implemented to reduce the severe outcomes related to infections and control the transmission in the care facilities.

Nevertheless, there are some limitations to this meta-analysis. Firstly, we were unable to estimate the long-term effectiveness of vaccines due to the limited length of follow-up. A test-negative case-control study conducted in England, protection of fully vaccinations with the Oxford-AstraZeneca vaccine in the elderly was maintained from the second week (VE=22.0%, 95%CI, 11.0 to 32.0) after vaccination to the end of the follow-up (more than 6 weeks) (VE=73.0%, 95%CI, 27.0 to 90.0)(Lopez Bernal et al., 2021). In the Mayo Clinic health system, the effectiveness after the second dose of the Pfizer-BioNTech vaccine or the Moderna vaccine increased from 53.6% (95%CI, 40.9 to 63.8) in the first week to 92.5% (95%CI, 70.2 to 99.1) in the sixth week(Pawlowski et al., 2021). Based on available evidence, there is increased VE within 6 weeks after full vaccination, but it is difficult to reveal the peak effectiveness and actual duration of immunization protection. Secondly, we didn't estimate the VE against infectiousness to others. A retrospective cohort study in the US suggested 80.0% (95%CI, 91.0 to 56.0) effectiveness against infectiousness to others after the second dose of the Pfizer-BioNTech vaccine(Tande et al., 2021). In addition, a single dose of the Moderna vaccine was estimated to reduce the potential transmission to others by 61.0% (95%CI, 31.0 to 79.0)(Lipsitch and Kahn, 2021). The vaccine could reduce the risk of transmission, but further studies are needed to assess the actual VE for every vaccine. Thirdly, the emergence of SARS-CoV-2 variants

caused increase severe infections(Gomez et al., 2021), and four dominant Variants of Concern (VOCs) were B.1.1.7 (Alpha, UK, Sep-2020), B.1.351 (Beta, South Africa, May-2020), P.1 (Gamma, Brazil, Nov-2020) and B.1.617.2 (Delta, India, Oct-2020)(WHO, 2021a). Several clinical trials have reported the vaccine effectiveness against variants(Haas et al., 2021). There was no effectiveness against mild-to-moderate Covid-19 due to B.1.351 variant (VE=21.9%, 95%CI, -49.9 to 59.8) after two doses of the ChAdOx1 nCoV-19 vaccine(Madhi et al., 2021). Nevertheless, two doses of the Pfizer-BioNTech vaccine showed 87.0% (95%CI, 81.8 to 90.7) effectiveness against the B.1.1.7 variant and 72.1% (95%CI, 66.4 to 76.8) against the B.1.351 variant(Abu-Raddad et al., 2021). And the VE for two doses of CoronaVac vaccine was 59.0 % (95%CI, 16.0 to 81.6) against the B.1.617.2 variant(Li et al., 2021). A single dose of the Ad26.COV2.S also showed 68.1% (95%CI, 48.8 to 80.7) effectiveness against the P.1 variant to prevent moderate to severe COVID-19(Sadoff et al., 2021). The estimates of VE against SARS-CoV-2 variants in real-world settings are scarce, so we are not yet to evaluate VE with the variants, what we need to do next.

Studies in the real-world around the world have shown that the proved vaccines are highly protective against SARS-CoV-2, therefore, we should be fully vaccinated according to the standard schedule to achieve maximum VE. It is worth noting that vaccination cannot eliminate the risk of infections(Brosh-Nissimov et al., 2021), and preventive and control measures should be taken seriously, especially for the high-risk groups.

Conclusions

Consistent with the results of phase III clinical trials, the authorized vaccines are highly protective against SARS-CoV-2 in the real-world settings. Besides, the actual VE depends on not only the effectiveness of the vaccine itself but also on the vaccinated population and status. Preventive measures remain essential.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical approval

This study does not require ethical approval because the meta-analysis is based on published research, and the original data are anonymous.

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Figure Legends:

Figure 1. Literature review results and inclusion criteria

Flow diagram of study selection for meta-analysis. 50 publications and 1 record reported the COVID-19 vaccine effectiveness among 14 countries from August 6, 2020 to October 6, 2021 were included in this meta-analysis.

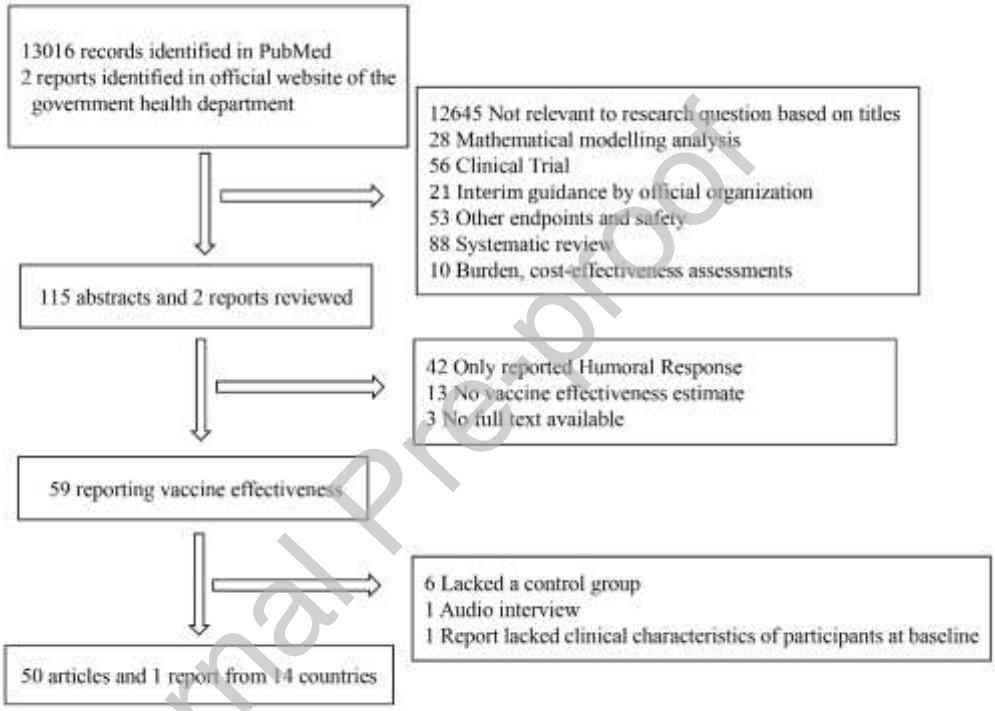

Figure 2. COVID-19 VE for prevention of SARS-CoV-2 infection in fully vaccinated status

Forest plot showing VE for prevention of SARA-CoV-2 infection for fully vaccinated populations, and a total of 35 studies contributed information on the effectiveness against SARA-CoV-2 infection.

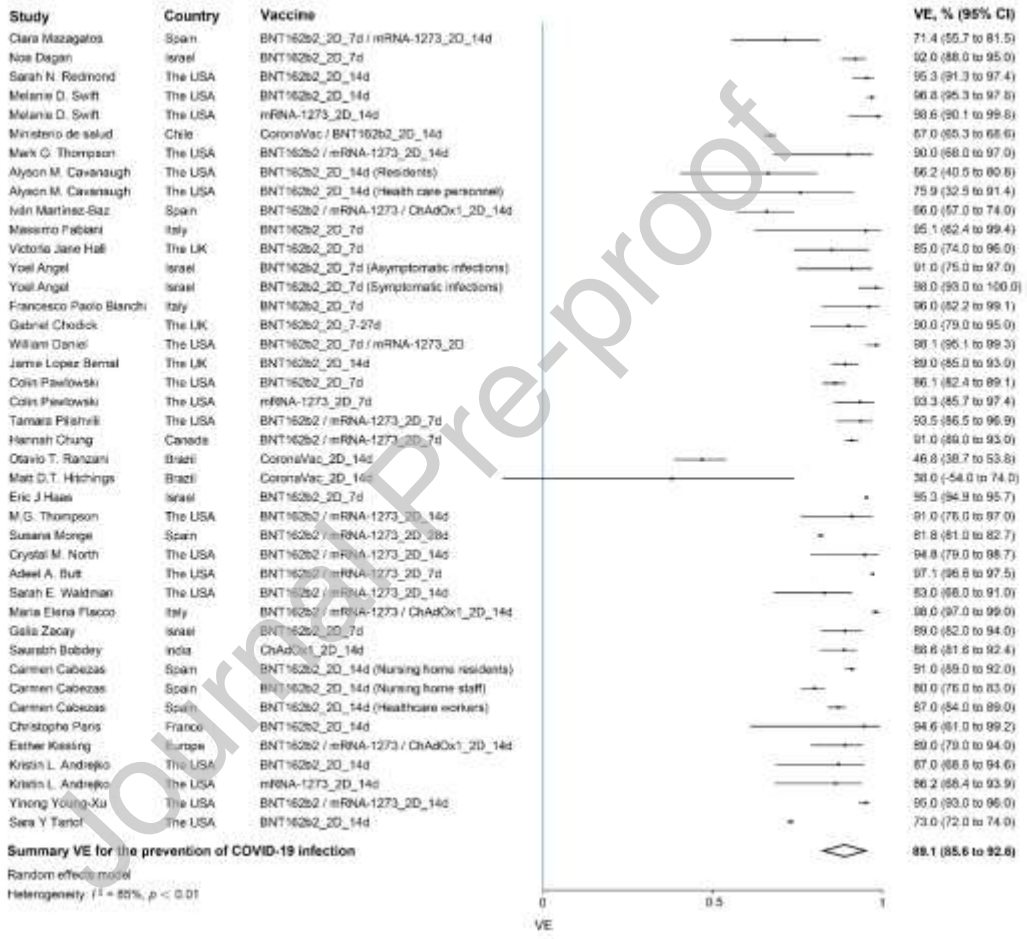

Figure 3. COVID-19 VE for prevention of COVID-19-related hospitalization, admission to the ICU and severe or critical hospitalization, and death in fully vaccinated status

Forest plot showing VE for prevention of COVID-19 related hospitalization, severe diseases and death for fully vaccinated populations, and a total of 15, 4, and 8 included studies contributed information on the effectiveness against COVID-19 related hospitalization, severe diseases, and death, respectively.

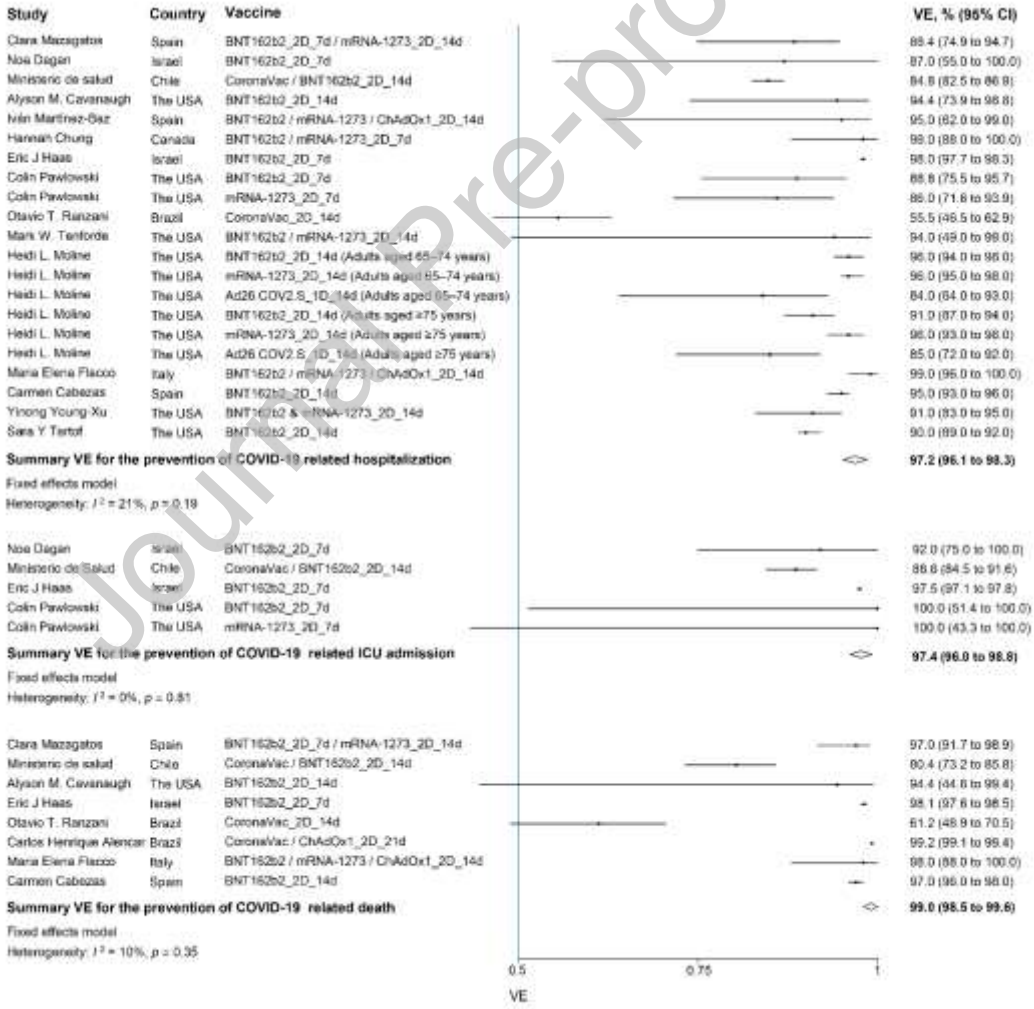

Figure 4. COVID-19 VE for prevention SARS-CoV-2 infection in different populations

Forest plot showing VE for prevention of SARA-CoV-2 infection for fully vaccinated populations based different population groups, and a total of 17, 15, and 11 included studies contributed information on the effectiveness against SARS-CoV-2 infection for healthcare workers (HCWs), the elderly, and general population aged 16 years or older, respectively.

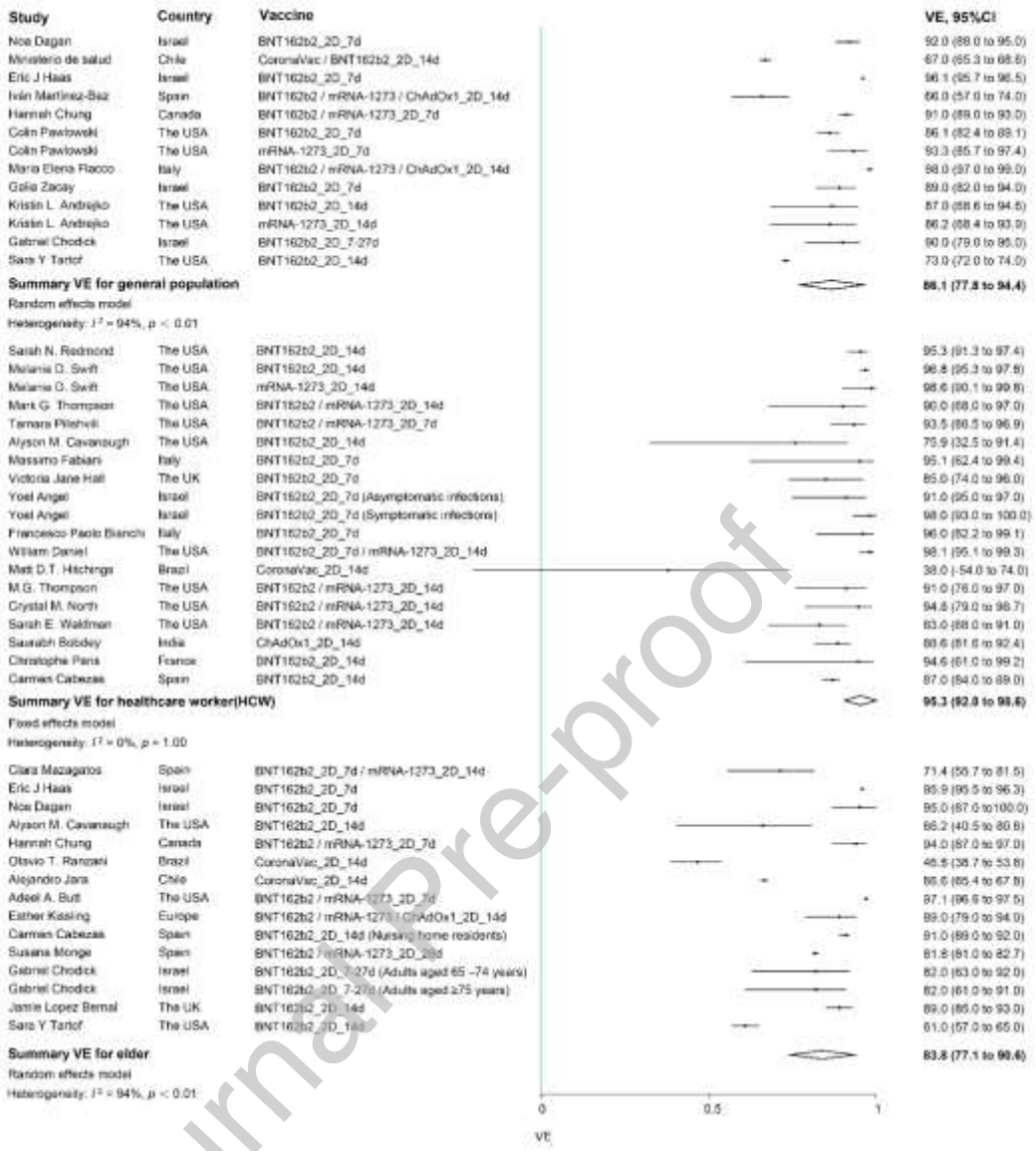

Figure 5. Summary VE against SARS-Cov-2 infection of different brands in full vaccination

Forest plot showing VE for prevention of SARA-CoV-2 infection for fully vaccinated populations with different vaccine brands, and a total of 23, 5, and 3 included studies contributed information on the effectiveness of the Pfizer-BioNTech, Moderna, and CoronaVac, respectively.

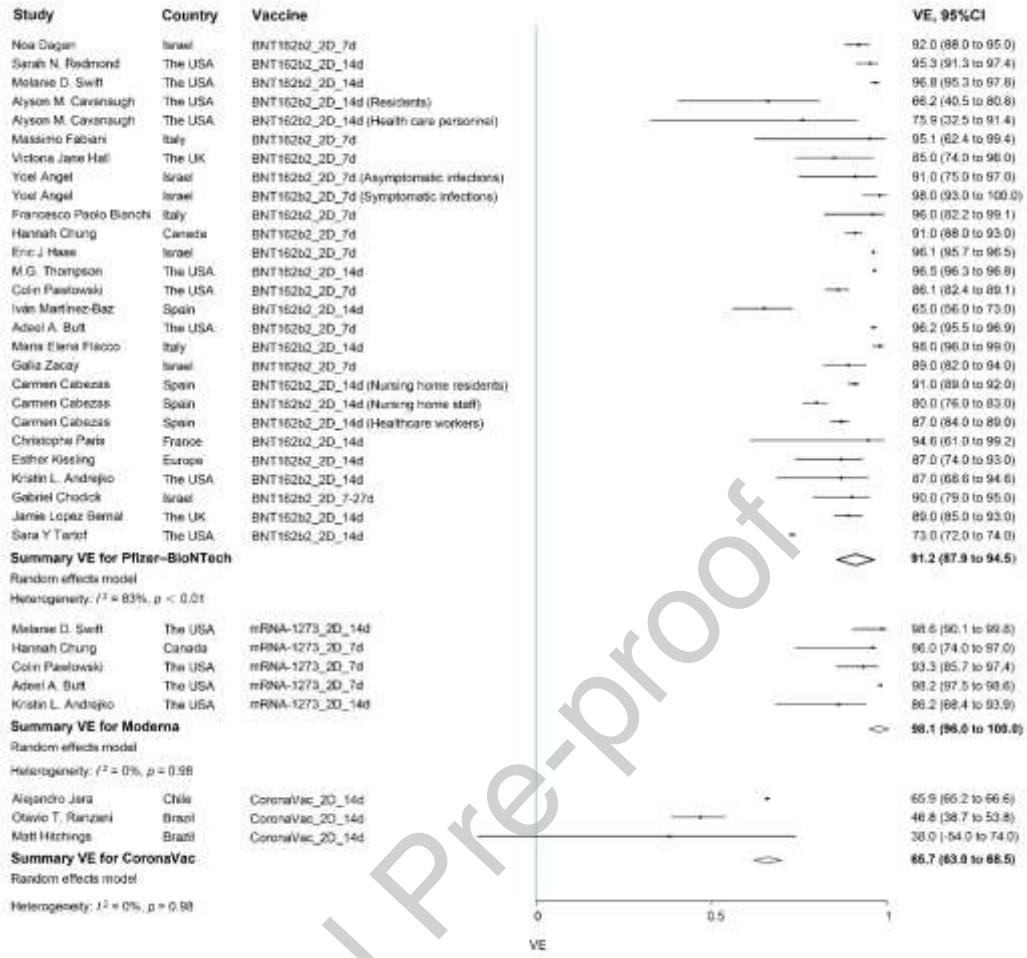

Figure 6. Summary VE against COVID-19-related hospitalization and death of the Pfizer-BioNTech vaccine among fully vaccinated individuals

Forest plot showing VE for prevention of COVID-19-related hospitalization and death of the Pfizer-BioNTech vaccine among fully vaccinated individuals, and a total of 9 and 3 included studies contributed information on the effectiveness against COVID-19-related hospitalization and death of the Pfizer-BioNTech vaccine.